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Original Article

Validation of Clinical Prediction Rules for Bone Marrow Involvement in Hodgkin Lymphoma

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ABSTRACT:

Bone marrow involvement (BMi) is observed in 5-6% of patients with Hodgkin lymphoma (HL). In the era of Positron Emission Tomography (PET/CT) bone marrow biopsy (BMb) can be omitted. However, if a baseline PET evaluation is not possible for various reasons, the prediction of BMi based on clinical characteristics is still relevant in order to avoid BMb in patients at low risk for BMi. Thus, we aimed to validate two clinical prognostic systems for BMi in HL. Based on our published prognostic system (Vassilakopoulos et al, Blood 2005), 539 patients with HL were retrospectively classified as low-, intermediate- and high-risk for BMi. In addition, patients were scored as 0, 1, 2, and 3-5 based on Levis' prognostic score (Clin Lymphoma Myeloma 2004). Among 539 patients, 31 (6%) had a positive BMb. According to the first prognostic system, 48%,32% and 20% of the patients were classified as low-, intermediate- and high-risk, with corresponding risks of BMi 0%, 4.1% and 21.8%, similar to the original publication. Among evaluable patients for Levis' prognostic system, 42%, 26%, 15% and 16% were scored as 0, 1, 2, 3-5, with corresponding frequency of BMi 0%,3.7%,9% and 16%, being also in agreement with the original publication. In conclusion, both clinical prognostic systems for BMi in HL were successfully validated. The first prognostic system appeared superior defining a larger subgroup of patients with minimal risk for BMi, in which BMb could be safely omitted. This can be particularly important whenever baseline PET/CT is cannot be performed.

KEY WORDS: *Bone marrow involvement, Hodgkin's lymphoma, Model, Prediction rule, Validation*

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INTRODUCTION

Bone marrow involvement (BMi) is observed in 4-14% of patients with Hodgkin lymphoma (HL).[1-8] Trephine biopsy has been the "gold standard" for the identification of BMi in HL for many years. Recent data demonstrate that bone BM biopsy can be omitted if patients are staged by

Positron Emission Tomography / Computed Tomography (PET/CT).[9] However, PET/CT may not be routinely available for baseline staging of HL in many patients even in the Western world. Since trephine biopsy is an invasive and potentially painful procedure, both the Ann-Arbor staging system and the Cotswolds meeting provide potential indications for restricting trephine biopsies to selected patients only. However, many practicing physicians routinely perform trephine biopsies in all patients with HL. In 2005 we constructed a clinical prediction rule with the aim to identify those patients with HL who are at minimal or at high risk for BMi.[10] Another prediction rule had also been developed by Levis et al. in 2004.[11]

In the present study we further assess the validity of these previously published clinical prediction rules in an independent population of patients with HL, who were diagnosed and staged after the end of our previous study. We also evaluated the impact of platelet count on the performance of our model, since this potentially important variable had not been systematically recorded in the previous study.[10]

PATIENTS AND METHODS

Between 2003 and 2014, 563 consecutive, unselected patients with biopsy-proven HL, aged ≥14 years old, were evaluated in order to receive first-line treatment in the Haematology Section of the First Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Greece (up to May 2008) and subsequently to the Department of Haematology, Medical School, National and Kapodistrian University of Athens, Greece; the First Department of Internal Medicine and the First Propedeutic Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Greece; or the Department of Haematology, Athens Medical Center, Psychikon, Athens, Greece. Patients were clinically staged according to the Ann-Arbor system12,13. Staging procedures included detailed history and physical examination, complete blood counts and biochemical profile, chest X-rays, computed tomography of the chest, abdomen and pelvis, and bone marrow biopsy. PET/CT was systematically adopted very recently (2009-2010). Bone marrow biopsy data were available in 541/563 patients (96.1%).

Information on the 6 variables included in our previously described model were retrospectively collected, namely: Age (< vs. ≥ 35 years), B-symptoms, clinical stage prior to bone marrow biopsy (CSPBM coded as I/II vs. III/IV), inguinal and/or iliac involvement, anemia (defined as hemoglobin <13g/dl for males and <11.5g/dl for females), and leukocyte counts (≥ vs. <6x10^9/l). Data on 4 additional variables included in the Levis' model (apart from B-symptoms, which were shared by both models) were also retrospectively collected: Infradiaphragmatic nodal involvement, liver involvement, number of involved nodal sites (≥4 vs. ≤3, according to the definition provided by Levis et al[11]), and histologic subtype (mixed cellularity or lymphocyte depletion vs. others). CS_{PBM} was defined as the clinical stage assigned to each patient after history, physical examination and conventional imaging procedures had been completed, but without knowledge of the results of bone marrow biopsy. PET/CT results were not taken into account in the minority of patients with available data. Platelet counts were also recorded in order to assess whether the discriminatory power of the models could be improved by adding this variable, since they had not been evaluated in our previous study. Full data for bone marrow biopsy results and the 6 variables of our model were available in 539/563 (95.7%) patients, who formed the working basis of the present report. Full data regarding the variables included in the Levis' model were available in 507 (90.0%) patients.

A score $Z_s = 8x_1+6x_2+5x_3+5x_4+3x_5+3x_6-8$ was assigned to each patient with complete data, as previously described. The values of x_1-x_6 are provided in Table 1. Patients were classified to 3 groups with different risk of BMi according to the value of Z_s: The low-risk group included patients with Z_s values <0, the standard-risk group included patients with Z_s values 0-9, and the high-risk group patients with Z_s values ≥10.

Levis' model was based on the number of adverse prognostic variables: 4 groups were defined according to the presence of 0, 1, 2 or 3-5 adverse variables.

Statistical analysis was based on descriptive methods. The correlation between prognostic variables and bone marrow involvement was based on the chi-square test or the Mann-Whitney test, as appropriate.

RESULTS

Frequency of Bone Marrow Involvement and Adverse Risk Factors

Among 539 patients with full data available, 31 (5.8%) had bone marrow involvement. The frequency of adverse prognostic features for BMi in this population is given in Table 2. B-symptoms (p<0.001), CSPBM III/IV (p<0.001), anemia (p<0.001), and inguinal/iliac involvement (p<0.001) were highly correlated with the probability of BMi; the associations with age ≥35 years (p=0.003) and WBC <6x109/l (p=0.03) were also statistically significant. With the exception of histologic subtype (p=0.16), all other Levis' model variables were highly correlated with the probability of BMI, i.e B-symptoms (p<0.001),

TABLE 1. Description of our clinical prediction rule for bone marrow involvement in Hodgkin lymphoma[10]. A score $Z_s = 8x_1+6x_2+5x_3+5x_4+3x_5+3x_6-8$ was assigned to each patient. The values of x_1-x_6 are provided in the table. Patients were classified to 3 groups with different risk of BMi according to the value of Z_s: Low-risk with Z_s values <0, standard-risk with Z_s values 0-9, and high-risk with Z_s values ≥10

Covariate	$x_i = 0$	$x_i = 1$	Simplified Coefficient
x_1: B-symptoms	absent	present	$b_{1s}=8$
x_2: Clinical stage prior to BMB	I/II	III/IV	$b_{2s}=6$
x_3: Anemia (hemoglobin; g/dL)	males ≥13 g/dL females ≥11.5 g/dL	males <13 g/dL females <11.5 g/dL	$b_{3s}=5$
x_4: Leukocyte counts	≥6x10^9/L	<6x10^9/L	$b_{4s}=5$
x_5: Age	< 35 years	≥ 35years	$b_{5s}=3$
x_6: Iliac/inguinal involvement	absent	present	$b_{6s}=3$
Constant			$b_{0s}=-8$

infradiaphragmatic nodal involvement (p<0.001), liver involvement (p<0.001), involvement of ≥4 nodal sites (p<0.001).

According to our model, 257 out of 539 patients (48%) were classified into the low-risk, 172 (32%) into the standard -risk and 110 (20%) into the high-risk group. According to Levis model, 214/507 (42%) patients had no adverse factors, 134 (26%) had 1, 78 (15%) had 2 and 81 (16%) had 3-5 adverse factors.

Validation of the Clinical Prediction Rules

Our previously described clinical prediction rule was very accurate in the classification of this patient population according to their predicted risk of BMi, as shown in Table 3: No case of BMi was observed among the 257 patients of the low-risk group; BMi was recorded in 7/172 standard-risk patients (4.1%) versus 24/110 (21.8%) patients of the high-risk group. These results are very similar to the original ones (Table 3).

Levis model was also accurate in predicting the risk of BMi, as shown in Table 4: No case of BMi was observed among the 214 patients of the low-risk group without risk factors; in the group of patients with 1 and 2 risk factors, BMi was recorded in 5/134 (3.7%) and 7/78 (9.0%) respectively versus 13/81 (16.0%) for the patients of the high-risk group (3-5 risk factors). These results are also similar to the original ones, as summarized in table 4, but the size of each subgroup is slightly different.

Effect of Platelet Counts

The median platelet counts were not significantly different between patients without and with BMi; they were 310x10^9/L (31-904) vs. 348x10^9/L (96-705) respectively (p=0.61, by the Mann-Whitney test). Abnormally low platelet counts, <140 x10^9/L, were recorded in 14 patients: 3 of them (21.4%) had BMi vs. 28/525 (5.3%) in patients with normal or high platelet counts (p=0.049 by Fisher's exact test). All 3 patients with BMi and a low platelet count had been already classified in the high-risk group for BMi by our model, based on the presence of other risk factors.

DISCUSSION

In the present study we validated the clinical prediction rules for BMi in HL, which were published by our group in 2005[10] and by Levis et al in 2004,[11] based on 6 and 5 simple clinical and laboratory parameters respectively. Overall, the incidence of BMi was 5.4% in keeping with data reported in the literature.[1-8,10-11]

The classification of patients into the low, intermediate and high risk groups was roughly similar to our original publication (Table 3).[10] More importantly, the risk of BMi for the patients classified in each group was virtually the same with the original study (Table 3): No patient of the low-risk group had BMi (vs. 0.3% in the original study) versus 4.8% of those classified in the standard-risk group (vs. 4.2% in the original study) and 19.8% of those classified in the high-risk group (vs. 25.5% in the original study).

In an attempt to further improve the performance of our model, we evaluated whether the addition of thrombocytopenia could be useful, since this parameter had not been included in the initial study even though its potential significance had been pointed out by other investigators:[1,4,8] Thrombocytopenia was very rare but the probability of BMI was higher in patients with plate-

TABLE 2. Frequency of bone marrow involvement according to the prognostic parameters included in the models under evaluation

		Frequency			
Clinical/Laboratory/Pathologic Parameter		**Patients (#)**	**Patients (%)**	**Bone Marrow Involvement [#,(%)]**	**p-value**
***Vassilakopoulos Model*[10]**					
B-Symptoms	no	361	67	5 (1.4%)	<0.001
	yes	178	33	26 (14.6%)	
Clinical stage pre BM	I/II	370	69	7 (1.9%)	<0.001
	III/IV	169	31	24 (14.2%)	
Anemia	no	309	57	2 (0.6%)	<0.001
	yes	230	43	29 (12.6%)	
White blood cell count	≥6x10^9/L	455	84	22 (4.8%)	0.03
	<6x10^9/L	84	16	9 (10.7%)	
Iliac/inguinal inv/ment	no	448	83	17 (3.8%)	<0.001
	yes	91	17	14 (15.4%)	
Age	<35 years	294	55	9 (3.1%)	0.003
	≥35 years	245	45	22 (9.0%)	
***Levis Model*[11]**					
B-Symptoms	no	361	67	5 (1.4%)	<0.001
	yes	178	33	26 (14.6%)	
Liver involvement	no	516	96	25 (4.8%)	<0.001
	yes	21	4	6 (28.6%)	
Infradiaphragmatic inv/ment	no	358	67	6 (1.7%)	<0.001
	yes	179	33	25 (14.0%)	
Nodal sites involved	<4	426	79	17 (4.0%)	<0.001
	≥4	110	21	14 (12.7%)	
Histology	NLP/LRC/NS	404	79	17 (4.2%)	0.16
	MC/LD	106	21	8 (7.5%)	

let counts <140x10^9/L (21.4% vs. 5.3% for patients with normal platelet counts). However, all 3 cases with mild thrombocytopenia and BMi had already been classified in the high-risk group, so that there was no evidence that the addition of this parameter could meaningfully improve the discriminative ability of the model.

The adequate validation of this clinical prediction rule further facilitates the omission of BM biopsy in approximately half of HL patients, who fall into the low-risk group. In fact, 257 biopsies were performed without a single positive result and the expected rate of positive biopsies in this group is predicted to be <1%. However, BM biopsy cannot be safely spared in the standard-risk and high-risk groups solely based on the application of the present prognostic tool.

The model described by Levis et al[11] was also adequately validated by this independent study, but the size of the low-risk group was smaller (42% vs. 48% of total patient population), thus permitting the omission of BM biopsy in an absolute percentage of 6% less HL patients. The high risk group was also somewhat smaller and the risk of BMi was also smaller compared to our definition (16.0% vs. 21.8%). However, this model incorporated histology, as assessed in a series of 1161 patients diagnosed

TABLE 3. Performance of the clinical prediction rule published by Vassilakopoulos et al[10] in the validation sample compared to the original one

Risk Group	Validation Sample		Original Sample	
	Frequency [# (%)]	**Risk of BMI [# (%)]**	**Frequency [# (%)]**	**Risk of BMI [# (%)]**
Low	257 (48%)	0/257 (0%)	646 (44%)	2/646 (0.3%)
Standard	172 (32%)	7/172 (4.1%)	544 (37%)	23/544 (4.2%)
High	110 (20%)	24/110 (21.8%)	290 (20%)	74/290 (25.5%)
Total	539 (100%)	31/539 (5.8%)	1480 (100%)	99/1480 (6.7%)

between 1982 and 2000, in which the frequency of mixed cellularity and lymphocyte depletion was 34%. The present validation sample included 539 patients diagnosed between 2003 and 2014 and the frequency of mixed cellularity and lymphocyte depletion histologies was only 21%. This is probably due to the gradual change of diagnostic criteria for HL subclassification during the 90's. This difference is mainly responsible for the higher percentage of low-risk patients in comparison to the original data of Levis model (42% vs 29%).[11]

Several studies have recently shown that PET/CT may reveal even more cases of BMi than BM biopsy does.[14-25] A recent meta-analysis of 955 patients demonstrated PET/CT sensitivity and specificity of 96.9% (95% CI: 93.0-99.0%) and 99.7% (98.9-100.0% respectively), while only 1.1% of the patients had a positive BMB despite a negative PET/CT.[26] The major study that contributed to this meta-analysis (454 patients) also suggested that 1.1% of the patients had positive BMB in the absence of positive PET/CT and that all of them were upstaged from stage III to IV without any impact on treatment strategy.[17] Two other large studies reported similar results, with 21/1085 (1.9%) and 1/832 (0.1%) of all patients having a positive bone marrow biopsy despite the absence of focal lesions on PET/CT. However, it should be noted that the criteria for bone marrow positivity by PET/CT were heterogenous in the studies included in the meta-analysis and 5/9 of them accepted diffuse BM uptake more than (or equal to) the liver as evidence of BMI in addition to focal uptake. Recent recommendations have adopted the omission of BMB in patients who have been staged by PET/CT,[9,27] since the few false negatives are typically seen in already advanced stage patients, thus being of minor clinical significance (reviewed in ref#28,29).[28,29]

It should be noted that even after the elimination of the need for BMB by the application of PET/CT in patients with HL, the latter still remains an expensive staging procedure, that may not be available in the developing countries. Furthermore, it may not be universally available even in the Western world due to geographic, logistic, insurance-related or other limitations. In such situations, the use of the described clinical prediction rules may permit the omission of BMB in approximately half of patients with HL, i.e. those who belong to the low-risk group and have a very low risk of BMi.

In conclusion, the clinical prediction rules described in 2004 and 2005 in order to stratify the risk of BMi in patients with HL appear to be valid in a large, independent patient series. This observation can encourage their application in the everyday practice and the present evaluation suggests that our 2005 clinical prediction rule may be the most suitable. This may be particularly useful in

TABLE 4. Performance of the clinical prediction rule published by Levis et al[11] in the validation sample compared to the original one

Risk Group	Validation Sample		Original Sample	
(Score)	**Frequency [# (%)]**	**Risk of BMI [# (%)]**	**Frequency [# (%)]**	**Risk of BMI [# (%)]**
0	214 (42%)	0/214 (0%)	331 (29%)	1/331 (0.3%)
1	134 (26%)	5/134 (3.7%)	364 (31%)	9/364 (2.5%)
2	78 (25%)	7/78 (9.0%)	225 (19%)	17/225 (7.6%)
3-5	81 (16%)	13/81 (16.0%)	241 (21%)	65/241 (27.0%)
Total	507 (100%)	25/507 (4.9%)	1161 (100%)	92/1161 (7.9%)

settings that cannot support PET/CT-based staging due to economic, geographic or other reasons, thus reducing patients' discomfort and health care costs in approximately 50% of HL cases.

Conflict of Interest: Honoraria-Advisory Board: Amgen, Novartis, Roche.

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